noven
PHARMACEUTICALS, INC.

January 19, 2005

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004P-0472: Comments of Noven Pharmaceuticals, Inc., on Supplement to Citizen Petition Regarding Approval of ANDA 76-258 for Generic Fentanyl Transdermal System

In response to the December 30, 2004 addendum submitted by Drs. Brookoff and Voth ("Petitioners") in the referenced proceeding, Noven Pharmaceuticals, Inc. ("Noven") submits the following supplemental comments. Noven relies on its prior Comments and will focus this supplemental submission on responding to only certain aspects of Petitioners' contentions.

1. While Petitioners dispute much of what Noven presented in its comments,[1] they make several concessions in their addendum which support Noven's argument that Duragesic® is subject to the same abuse potential to which Petitioners speculate generic formulations may be subject. Specifically, Petitioners point to actual evidence that the Duragesic® patch can rapidly transmit fentanyl into the bloodstream when placed and held against the inside of the cheek (at 11). Thus, Petitioners admit that, if anything, Duragesic® has the same risk of transmucosal abuse they claim for generic matrix formulations. Petitioners also concede that "fentanyl gel extracted from the Duragesic® patch can be absorbed through the mucosa inside the cheek" (at 15). These concessions confirm Noven's point: there is no evidence that the risk of abuse of generic fentanyl transdermal products is any greater than that of Duragesic®.

2. In addressing the standard for ANDA approval, Petitioners incorrectly assert that generic manufacturers must prove that their products are not subject to potential abuse as part of the ANDA approval process. The law does not place this burden on generic manufacturers. Once a reference drug has been approved, an ANDA applicant need only establish bioequivalence and sameness of dosage form, route of administration, active ingredients and labeling in order to obtain approval because the safety and efficacy of the

[1] For example, Petitioners criticize Noven's discussion of freezing of Duragesic® and ask for Noven's source (at 16). Noven's source is a DEA article cited by Petitioners in their own Citizen Petition, which is available on DEA's website. Petitioners reject Noven's claim that the DEA article is an "unimpeachable" source, even though Petitioners are willing to rely instead on personal statements made to them by unidentified DEA agents. It is stunning that Petitioners criticize Noven's citation of reliable, published governmental sources but demand that FDA accept their undocumented and conclusory speculation as if it were scientific dogma.

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reference product have already been established. As here, in the absence of any evidence that the generic formulation will be unsafe, FDA should approve an ANDA that satisfies the FDCA's enumerated requirements. *See* Noven Comments at 4-5, 21-22.

Petitioners argue that additional proof is appropriate in the context of approval of opioids like fentanyl, which are subject to potential abuse. This proposal ignores the fact that Congress has addressed these concerns through the existing statutory framework.

As Petitioners note, in the Controlled Substances Act ("CSA") Congress authorized FDA, in conjunction with DEA, to classify and list drugs as controlled substances, and to require heightened measures to prevent abuse and diversion of listed drugs. The CSA existed when Congress passed the Hatch-Waxman amendments; Congress did not at that time or any time since authorize FDA to require ANDA applicants to provide clinical evidence of lack of potential abuse of their formulations of those products. Indeed, it was through the CSA that Congress wanted to deal with products potentially subject to abuse; there is no new situation that Congress did not consider when it passed either the CSA or the Hatch-Waxman amendments. Congress previously balanced and determined the factors it believed to be appropriate for consideration of approval of an ANDA and for controlling abuse and diversion of particular drugs. Petitioners' desire that FDA adopt additional requirements simply does not trump Congress' careful balancing of these interests.

3. Petitioners also chastise Noven for purportedly citing no scientific evidence to support its statements. As discussed above, the FDCA obligates Noven to prove bioequivalence with the innovator; that evidence is contained in proprietary information submitted with Noven's ANDA. The fact that Petitioners are not privy to those data does not change the sufficiency of the data. Having presented its data to FDA, Noven has no further independent obligation to refute speculation made in a citizen petition. Indeed, it is the petitioners' obligation to present concrete evidence to justify the relief they request.

Yet, despite their conclusory dismissal of Noven's arguments, the fact remains that Petitioners have cited no scientific data to support their "contentions" and "belief" that generic formulations of fentanyl transdermal will be subject to greater abuse than Duragesic®. In fact, they candidly concede in numerous instances that their claims are merely speculation about how the matrix formulation may work because they have no evidence to prove that these generic formulations have a higher risk for abuse. Instead, Petitioners demand that Noven and others be required to undertake studies to prove the negative: that their product will not be abused. Not only is such proof inconsistent with FDA's requirements, it would be impossible to present evidence that a schedule II listed drug is not subject to abuse; Duragesic® itself is abused. Moreover, any such requirement would obligate a generic manufacturer to prove more than the innovator and would be inconsistent with the purpose of the Hatch-Waxman amendments.

4. Finally, Petitioners' continual comparisons to OxyContin® are specious and a red herring. Attempting to inject the issues surrounding that controversial product into a debate about a product that simply does not have the same potential for abuse is misplaced. Unlike OxyContin®, there has been no evidence of a significant level of abuse of transdermal fentanyl in the almost 15 years it has been on the market nor any suggestion that the branded

manufacturer should develop or implement an RMP for Duragesic®. In any event, Petitioners are simply wrong that FDA could or did require generic manufacturers of extended-release oxycodone to implement RMPs as a condition of ANDA approval.

It goes without saying that, contrary to the Petitioners' suggestion (at 16), neither Noven nor Endo Pharmaceuticals, Inc., Noven's marketing partner, would seek approval of a product that it believed to be unsafe. Drs. Brookoff and Voth have not presented any evidence that generic fentanyl transdermal patches will be unsafe, much less any recognized or acceptable legal or scientific basis for FDA's refusing to approve ANDAs for such products that have established bioequivalence. As a result, granting the relief Petitioners request would undermine Congress' goals in the Hatch-Waxman amendments in the absence of any proper support, and their petition should be denied.

Respectfully submitted,

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